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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Richard A. SCHUMACHER et al.

Serial No. : 10/622,833 Group Art Unit: unknown

Filed : July 21, 2003 Examiner: unknown

For : PHOSPHODIESTERASE 4 INHIBITIORS, INCLUDING N-SUBSTITUTED ANLINE AND DIPHENYLAMINE ANALOGS

REQUEST FOR RECONSIDERATION

Mail Stop Conversion
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Decision on Petition dated September 21, 2004 (copy attached), wherein applicants request the above-identified application be accorded to the filing date of July 21, 2003, with the pages 51-74 of specification as part of the original disclosure.

Applicants hereby submit the omitted pages 51-74 of the specification (description and claims) in connection with the above-identified application. Please make the omitted pages of record.

Respectfully submitted,

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AJZ:ssr

cognitive impairment and/or in the treatment of psychosis, e.g., other PDE4 inhibitors, calcium channel blockers, chloinergic drugs, adenosine receptor modulators, amphakines NMDA-R modulators, mGluR modulators, and cholinesterase inhibitors (e.g., donepezil, rivastigimine, and glanthanamine). In such combinations, each active ingredient can be administered either in accordance with their usual dosage range or a dose below their usual dosage range.

The dosages of the compounds of the present invention depend upon a variety of factors including the particular syndrome to be treated, the severity of the symptoms, the route of administration, the frequency of the dosage interval, the particular compound utilized, the efficacy, toxicology profile, pharmacokinetic profile of the compound, and the presence of any deleterious side-effects, among other considerations.

The compounds of the invention are typically administered at dosage levels and in a mammal customary for PDE4 inhibitors such as those known compounds mentioned above. For example, the compounds can be administered, in single or multiple doses, by oral administration at a dosage level of, for example, 0.01-100 mg/kg/day, preferably 0.1-70 mg/kg/day, especially 0.5-10 mg/kg/day. Unit dosage forms can contain, for example, 0.1-50 mg of active compound. For intravenous administration, the compounds can be administered, in single or multiple dosages, at a dosage level of, for example, 0.001-50 mg/kg/day, preferably 0.001-10 mg/kg/day, especially 0.01-1 mg/kg/day. Unit dosage forms can contain, for example, 0.1-10 mg of active compound.

In carrying out the procedures of the present invention it is of course to be understood that reference to particular buffers, media, reagents, cells, culture conditions and the like are not intended to be limiting, but are to be read so as to include all related materials that one of ordinary skill in the art would recognize as being of interest or value in the particular context in

which that discussion is presented. For example, it is often possible to substitute one buffer system or culture medium for another and still achieve similar, if not identical, results. Those of skill in the art will have sufficient knowledge of such systems and methodologies so as to be able, without undue experimentation, to make such substitutions as will optimally serve their purposes in using the methods and procedures disclosed herein.

The present invention will now be further described by way of the following non-limiting examples. In applying the disclosure of these examples, it should be kept clearly in mind that other and different embodiments of the methods disclosed according to the present invention will no doubt suggest themselves to those of skill in the relevant art.

In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius; and, unless otherwise indicated, all parts and percentages are by weight.

The entire disclosures of all applications, patents and publications, cited above and below, are hereby incorporated by reference.

EXAMPLE 1A

1-Cyclopentyloxy-2-methoxy-5-nitrobenzene

To a suspension of 2-methoxy-5-nitrophenol (525g, 3.104 mol) and potassium carbonate (643.5g, 4.66 mol) in dimethylformamide (1 L), under N_2 protection, was added cyclopentyl bromide (499.2 mL, 4.66 mol). The suspension was heated to 100°C for 6h. Potassium carbonate (85.8g, 0.62 mol) and cyclopentyl bromide (50 mL, 0.46 mol) were added. The suspension was heated to 100°C for 4h. TLC indicated the reaction was complete (9:1 DCM:MeOH). The reaction mixture was cooled to room temperature and diluted with water (3L) and ether (3L). The layers were separated and the aqueous layer was re-extracted with ether (2L). The combined organic layers were washed with 1N NaOH (2L), water (2L), and brine

(2L). The organic layer was dried over sodium sulfate, filtered, and evaporated. The resulting solid was azeotroped with toluene (2 x 300 mL) to obtain 736.7g (99.6% yield) as a yellow solid.

The following compounds were prepared in a similar manner as described above:

a) 1-Cyclopropylmethoxy-2-methoxy-5-nitrobenzene

b) 1-Cyclopentoxy-2-difluoromethoxy-5-nitrobenzene

c) 1-Cyclopropylmethoxy-2-difluoromethoxy-5-nitrobenzene

EXAMPLE 1B

2-Methoxy-5-nitro-1-((3*R*)-tetrahydrofuryloxy)benzene

To a mixture of 2-Methoxy-5-nitrophenol (1.69 g, 10 mmol), triphenylphosphine (5.24 g, 20 mmol) and 3-(R)-hydroxytetrahydrofuran (1.80 g, 20 mmol) in anhydrous tetrahydrofuran (40 mL) was added drop-wise, with stirring, diisopropylazodicarboxylate (4.0 mL, 20 mmol) and the mixture was allowed to stir at room temperature for 16 h. The mixture was diluted with ether (150 mL) and washed with 2N NaOH (3 x 50 mL) and brine (50 mL), (MgSO4) and concentrated in vacuo. The crude residue was purified by flash column chromatography over silica gel (Biotage Flash 40M) eluting with 20% ethyl acetate in hexanes to give 1.05 g of product

The following compounds were prepared in a similar manner as described above:

a) 2-Methoxy-5-nitro-1-(3-tetrahydrofuryloxy)benzene

b) 2-Methoxy-5-nitro-1-((3*S*)-tetrahydrofuryloxy)benzene

c) 2-Difluoromethoxy-5-nitro-1-(3-tetrahydrofuryloxy)benzene

d) 2-Difluoromethoxy-5-nitro-1-((3*R*)-tetrahydrofuryloxy)benzene

e) 2-Difluoromethoxy-5-nitro-1-((3*S*)-tetrahydrofuryloxy)benzene

f) 2-Methoxy-5-nitro-1-(3-phenpropyloxy)benzene

g) 1-(2-Indanyloxy)-4-methoxy-5-nitrobenzene

EXAMPLE 1C

1-(*tert*-Butyldimethylsilyl)oxy-2-methoxy-5-nitrobenzene

To a mixture of 2-methoxy-5-nitrophenol (1.53 g, 9.0 mmol) and imidazole (1.08 g, 15.9 mmol) in anhydrous DMF (40 mL) was added, with stirring, *tert*-butyldimethylsilyl chloride (2.05 g, 13.6 mmol) and the mixture was allowed to stir at room temperature for 16 h. The solvent was removed *in vacuo* and the residue was dissolved in 40 mL of 50% ethyl acetate in hexanes and filtered through 10 g of silica gel. The silica gel was washed with an additional 200 mL of 50% ethyl acetate in hexanes and the filtrates were combined and concentrated *in vacuo* to give 2.01 g of product as a tan crystalline solid. ^{1}H NMR ($CDCl_3$) δ 7.89 (dd, 1H, J = 9.0 Hz, 2.8 Hz), 7.69 (d, 1H, J = 2.8 Hz), 6.88 (d, 1H, J = 9.0), 3.90 (s, 3H), 1.00 (s, 9H), 0.18 (s, 6H).

EXAMPLE 2

3-Cyclopentyloxy-4-methoxyaniline

To a suspension of 10% Pd on activated carbon (25g) in ethanol (4L), under N_2 protection, was added 1-cyclopentyloxy-2-methoxy-5-nitrobenzene (250g, 1.054 mol). The reaction mixture was degassed under vacuum three times. The reaction mixture was stirred vigorously while hydrogen gas was allowed to flow over the reaction mixture. After 4h the reaction was complete by TLC (5:1 hex:EA). The reaction mixture was filtered through a pad of celite and the celite was rinsed with additional ethanol. The solvent was removed in-vacuo to obtain 208.38g (95% yield) of 3-cyclopentyloxy-4-methoxyaniline as a red liquid. ^{1}H NMR

($CDCl_3$) δ 6.85 (d. J = 8.4Hz, 1H), 6.29 (s, 1H), 6.19 (dd, J = 2.8, 8.4, 1H), 4.69 (p, J = 4.4 Hz, 1H), 3.75 (s, 3H), 3.44 (bs, 2H), 1.90-1.81 (m, 6H), 1.61-1.55 (m, 2H).

The following compounds were prepared in a similar manner as described above:

a) 3-Cyclopentyloxy-4-difluoromethoxyaniline

b) 3-Cyclopropylmethoxy-2-methoxyaniline

c) 3-Cyclopropylmethoxy-4-difluoromethoxyaniline

d) 4-Methoxy-3-((3*R*)-tetrahydrofuryloxy)aniline

e) 4-Methoxy-3-(tetrahydrofuryloxy)aniline

f) 4-Methoxy-3-((3*S*)-tetrahydrofuryloxy)aniline

g) 4-Difluoromethoxy-3-(3-tetrahydrofuryloxy)aniline

h) 4-Difluoromethoxy-3-((3*R*)-tetrahydrofuryloxy)aniline

i) 4-Difluoromethoxy-3-((3*S*)-tetrahydrofuryloxy)aniline

j) 3-(*tert*-Butyldimethylsilyl)oxy-4-methoxyaniline

k) 4-Methoxy-3-(3-phenpropyloxy)aniline

l) 3-(2-Indanyloxy)-4-methoxyaniline

EXAMPLE 3

3-Cyclopentyl-4-methoxy-*N*-(3-pyridylmethyl)aniline

To a mixture of 3-pyridinecarboxaldehyde (106.55g, 0.995 mol) in methanol (5L) was added 3-cyclopentyloxy-4-methoxyaniline (208.38g, 1.005 mol) and p-toluenesulfonic acid monohydrate (200 mg). The reaction mixture was stirred for 4h. The flask was then cooled to 0°C and sodium borohydride (37.64g, 2.3 mol) was added portionwise over 4h. The reaction mixture was allowed to warm to room temperature over 16h with stirring. TLC indicated the reaction was complete (1:3 hex:EA). The solvent was evaporated until approximately 0.5L of

slurry remained. The slurry was diluted with water (1L) and extracted with ethyl acetate (2 x 2L). The combined organic layers were washed with brine (500 mL), dried over sodium sulfate, and concentrated to yield 300g (100% yield) of the desired product as a brown viscous liquid. 1H NMR (CDCl3) δ 8.61-8.48 (m, 2H), 7.69-7.67 (m, 1H), 7.24-7.21 (m, 1H), 6.72 (d. J = 8.4 Hz, 1H), 6.23 (s, 1H), 6.13 (dd, J = 2.6, 8.6, 1H), 4.65 (bs, 1H), 4.27 (s, 2H), 4.0 (bs, 1H), 3.73 (s, 3H), 1.88-1.70 (m, 6H), 1.65-1.45 (m, 2H).

The following compounds were prepared in a similar manner as described above:

a) 3-Cyclopentyloxy-4-methoxy-*N*-(3-thienylmethyl)aniline

b) 3-Cyclopentyloxy-4-methoxy-*N*-(4-pyridylmethyl)aniline

c) 3-Cyclopentyloxy-*N*-(2,6-dichloro-4-pyridylmethyl)- 4-methoxyaniline

d) 3-Cyclopentyloxy-4-methoxy-*N*-(2-quinolinylmethyl)aniline

e) 3-Cyclopentyloxy-4-methoxy-*N*-(3-quinolinylmethyl)aniline

f) 3-Cyclopentyloxy-4-methoxy-*N*-(4-quinolinylmethyl)aniline

g) 3-Cyclopentyloxy-4-methoxy-*N*-(2-pyrazinylmethyl)aniline

h) 4-Methoxy-*N*-(3-pyridylmethyl)-3-(3-tetrahydrofuryloxy)aniline

i) 4-Methoxy-*N*-(3-pyridylmethyl)-3-((3*R*)-tetrahydrofuryloxy)aniline

j) 4-Methoxy-*N*-(3-pyridylmethyl)-3-((3*S*)-tetrahydrofuryloxy)aniline

k) 3-Cyclopropylmethoxy-4-difluoromethoxy-*N*-(3-pyridylmethyl)aniline

l) 3-Cyclopentyloxy-4-difluoromethoxy-*N*-(3-pyridylmethyl)aniline

m) 4-Difluoromethoxy-*N*-(3-pyridylmethyl)-3-(3-tetrahydrofuryloxy)aniline

n) 4-Difluoromethoxy-*N*-(3-pyridylmethyl)-3-((3*R*)-tetrahydrofuryloxy)aniline

o) 3,4-Bis(difluoromethoxy)-*N*-(3-pyridylmethyl)aniline

p) 3-tert-Butyldimethylsilyloxy-4-methoxy-*N*-(3-pyridylmethyl)aniline

q) 3-Cyclopentyloxy-4-methoxy-*N*-(2-pyridylmethyl)aniline

r) 3-Cyclopentyloxy-4-methoxy-*N*-[1-(2-phenethyl)]aniline

s) *N*-Benzyl-3-cyclopentyloxy-4-methoxyaniline

t) *N*-[(Cyclohex-1-en-1-yl)methyl]-3-cyclopentyloxy-4-methoxyaniline

u) 3-Cyclopentyloxy-4-methoxy-*N*-(3,4,5-trimethoxybenzyl)aniline

v) *N*-[(Cyclohex-3-en-1-yl)methyl]-3-cyclopentyloxy-4-methoxyaniline

w) 3-Cyclopentyloxy-4-methoxy-*N*-(2,4,6-trimethylbenzyl)aniline

x) 3-Cyclopentyloxy-4-methoxy-*N*-(2-methylbenzyl)aniline

y) 3-Cyclopentyloxy-4-methoxy-*N*-(2-trifluoromethylbenzyl)aniline

z) 3-Cylclopentyloxy-4-methoxy-*N*-((3,4-methylenedioxy)benzyl)aniline

aa) 3-Cyclopentyloxy-*N*-(2-hydroxy-3-methoxylbenzyl)-4-methoxyaniline

bb) 3-Cyclopentyloxy-*N*-(3-furylmethyl)-4-methoxyaniline

cc) 3-Cyclopentyloxy-4-methoxy-*N*-(3-methylbenzyl)aniline

dd) 3-Cyclopentyloxy-4-methoxy-*N*-(2-methoxybenzyl)aniline

ee) 3-Cyclopentyloxy-4-methoxy-*N*-(3-chlorobenzyl)aniline

ff) 3-Cyclopentyloxy-4-methoxy-*N*-(3-methoxybenzyl)aniline

gg) 3-Cyclopentyloxy-4-methoxy-*N*-(2-chlorobenzyl)aniline

hh) 3-Cyclopentyloxy-4-methoxy-*N*-(3-methylbenzyl)aniline

ii) 4-Methoxy-3-(3-phenpropyloxy)-*N*-(4-pyridylmethyl)aniline

jj) *N*-(2,6-Dichloro-4-pyridylmethyl)-3-(2-indanyloxy)-4-methoxyaniline

kk) 4-Methoxy-3-(3-phenpropyloxy)-*N*-(2-pyridylmethyl)aniline

ll) *N*-(2,6-Dichloro-4-pyridylmethyl)-4-methoxy-3-(3-phenpropyloxy)aniline

mm) 4-Methoxy-3-(3-phenpropyloxy)-*N*-(3-pyridylmethyl)aniline

nn) 3-Cyclopentyloxy-4-methoxy-*N*-(2-thienylmethyl)aniline

oo) 3-(2-Indanyloxy)-4-methoxy-*N*-(3-thienylmethyl)aniline

pp) 4-Methoxy-3-(3-phenpropyloxy)-*N*-(3-thienylmethyl)aniline

qq) 3-(2-Indanyloxy)-4-methoxy-*N*-(2-pyridylmethyl)aniline

rr) 3-(2-Indanyloxy)-4-methoxy-*N*-(3-pyridylmethyl)aniline

ss) 3-(2-Indanyloxy)-4-methoxy-*N*-(4-pyridylmethyl)aniline

tt) 3-Cyclopentyloxy-4-methoxy-*N*-(3-piperidinemethyl)aniline

uu) 3-Cyclopentyloxy-4-methoxy-*N*-(3-(1-*tert*-butyloxycarbonyl)piperidinemethyl)aniline

vv) 3-Cyclopentyloxy-4-methoxy-*N*-(6-methyl-2-pyridylmethyl)aniline

ww) *N*-(2-Chloro-3-pyridylmethyl)-3-cyclopentyloxy-4-methoxyaniline

xx) *N*-(2-Chloro-5-pyridylmethyl)-3-cyclopentyloxy-4-methoxyaniline

yy) 3-Cyclopentyloxy-4-methoxy-*N*-(2-thiazolylmethyl)aniline

zz) 4-Methoxy-3-(3R)-tetrahydrofuranyloxy-N-(5-(1,3-dimethylpyrazolylmethyl)aniline

aaa) 4-Methoxy-3-(3R)-tetrahydrofuranyloxy-N-[4-(2,6-dichloropyridyl)]aniline

bbb) 3-Cyclopentoxy-4-methoxy-N-(2,6-difluorobenzyl)aniline

ccc) 3-Cyclopentoxy-4-methoxy-N-[4-(3,5-dimethylisoxazolyl)]aniline

ddd) 3-Cyclopentyloxy-4-methoxy-N-cyclohexylaniline (MW 289.416)

EXAMPLE 4

4-(N-piperidinylmethyl)iodobenzene

To a mixture of 0.31 g of piperidine (3.6 mmol) and 0.47 g of N,N-diisopropylethylamine 3.6 mmol) in 10 mL of dichloromethane was added 0.90 g of 4-iodobenzylbromide (3 mmol). The mixture was allowed to stir for 16 h and partitioned between 50 mL of EtOAc and 50 mL of water. The layers were separated and the EtOAc was washed with 25 mL of brine, dried

($MgSO_4$) and concentrated in vacuo to give 0.90 g of 4-(N-piperidinylmethyl)iodobenzene.. The product was used without further purification.

The following compounds were prepared in a similar manner as described above:

4-(N-morpholinomethyl)iodobenzene

4-(N,N-diethylaminomethyl)iodobenzene

EXAMPLE 5

5-Fluoro-3-pyridinecarboxaldehyde

To a mixture of 3.5 g of ethyl 5-fluoronicotinate (21 mmol) in 80 mL of dry toluene at -78°C under nitrogen was added 42 mL of 1.0M DIBAL in toluene dropwise with stirring. The mixture was stirred at -78°C for 3h and the excess DIBAL was quenched by adding 0.5 mL of EtOAc. The mixture was allowed to warm to room temperature and 100 mL of water was added. The mixture was filtered through celite and the filter cake washed with 3 X 10 mL of toluene. The layers were separated and the organic phase was washed with brine, dried ($MgSO_4$) and loaded onto a column (silica gel). The product was purified by eluting with 20%-35% EtOAc in hexanes to give 700 mg of 5-fluoro-3-pyridinecarboxaldehyde and 2.0 g of un-reacted starting material.

EXAMPLE 6

3-Cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

To a 100 mL oven dried, argon flushed flask was added in the following order 0.59 g (6.10 mmol) of NaOtBu, 360 mg of Pd2dba3, 20 mL of toluene, 0.14 mL of P(tBu)3, and a 20 mL solution of 1.3 g (4.36 mmol) of N-(3-pyridylmethyl)-3-cyclopentyloxy-4-methoxyaniline in toluene. With stirring, 3.1 g (15 mmol) of iodobenzene was added dropwise and the mixture

was stirred for 18 hours. The reaction mixture was diluted with EtOAc and washed twice with H2O and extracted with 3 x 15 mL of 3N HCl. The combined acid extracts were washed with 15 mL of EtOAc and then carefully neutralized with 6N NaOH to pH greater than 12. The basic solution was extracted with 2 x 15 mL of EtOAc and the combined organic fractions were subsequently washed with 15 mL of H2O and brine, dried (MgSO4), and concentrated. The residue was purified by chromatography over silica gel (Biotage Flash 40M) eluting with 25% EtOAc in hexanes. The material was further purified by crystallization from hexanes to give 550 mg of a white solid. 1H NMR (CDCl3) δ 8.61 (s, 1H), 8.49 (d, 1H, J = 4.2 Hz), 7.67 (d, 1H, 7.9 Hz), 7.30-7.10 (m, 3H), 6.90-6.80 (m, 4H), 6.80-6.60 (m, 2H), 4.94 (s, 2H), 4.64 (p, 1H, J = 4.1 Hz),3.84 (s, 3H), 1.86-1.70 (m, 6H), 1.65-1.45 (m, 2H).

The following compounds were prepared in a similar manner as described above:

a) 3-Cyclopentyloxy-4-methoxy-2'-methyl-*N*-(3-pyridylmethyl)diphenylamine

b) 3-Cyclopentyloxy-4-methoxy-3'-methyl-*N*-(3-pyridylmethyl)diphenylamine

c) 3-Cyclopentyloxy-4-methoxy-4'-methyl-*N*-(3-pyridylmethyl)diphenylamine

d) 3-Cyclopentyloxy-4'-ethyl-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

e) 3'-Chloro-3-cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

f) 4'-Chloro-3-cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

g) 3-Cyclopentyloxy-2',4-dimethoxy-*N*-(3-pyridylmethyl)diphenylamine

h) 3-Cyclopentyloxy-3',4-dimethoxy-*N*-(3-pyridylmethyl)diphenylamine

i) 3-Cyclopentyloxy-4,4'-dimethoxy-*N*-(3-pyridylmethyl)diphenylamine

j) 3-Cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)-3'-trifluoromethyldiphenylamine

k) 3-Cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)-4'-trifluoromethyldiphenylamine

l) 3-Cyclopentyloxy-3'-fluoro-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

m) 3-Cyclopentyloxy-4'-fluoro-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

n) 3-Cyclopentyloxy-4-methoxy-3'-phenyl-*N*-(3-pyridylmethyl)diphenylamine

o) 3-Cyclopentyloxy-4-methoxy-4'-phenyl-*N*-(3-pyridylmethyl)diphenylamine

p) 3'-Cyano-3-cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

q) 4'-Cyano-3-cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

r) Ethyl *N*-(3-cyclopentyloxy-4-methoxyphenyl)-*N*-(3-pyridylmethyl)-3-aminobenzoate

s) Ethyl *N*-(3-cyclopentyloxy-4-methoxyphenyl)-*N*-(3-pyridylmethyl)-4-aminobenzoate

t) 3-Cyclopentyloxy-4-methoxy-3'-nitro-*N*-(3-pyridylmethyl)diphenylamine

u) 3-Cyclopentyloxy-4-methoxy-4'-nitro-*N*-(3-pyridylmethyl)diphenylamine

v) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-*N*-(3-pyridylmethyl)-1-naphthylamine

w) 3-Cyclopentyloxy-2',3'-dimethyl-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

x) 3-Cyclopentyloxy-2',4'-dimethyl-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

y) 3-Cyclopentyloxy-2',5'-dimethyl-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

z) 3-Cyclopentyloxy-3',4'-dimethyl-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

aa) 3-Cyclopentyloxy-2',3'-dichloro-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

bb) 3-Cyclopentyloxy-3',4'-dichloro-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

cc) 3-Cyclopentyloxy-3',5'-dichloro-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

dd) 3'-Chloro-3-cyclopentyloxy-4'-fluoro-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

ee) 4'-Chloro-3-cyclopentyloxy-3'-fluoro-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

ff) 4'-Chloro-3-cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)-3'-trifluoromethyldiphenylamine

gg) 3-Cyclopentyloxy-4-methoxy-*N*-(3-thienylmethyl)diphenylamine

hh) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-*N*-(3-thienylmethyl)-1-naphthylamine

ii) 3-Cyclopentyloxy-2',3'-dichloro-4-methoxy-*N*-(3-thienylmethyl)diphenylamine

jj) 3-Cyclopentyloxy-4-methoxy-4'-methyl-*N*-(4-pyridylmethyl)diphenylamine

kk) 3-Cyclopentyloxy-*N*-(2,6-dichloro-4-pyridylmethyl)-4-methoxy-3'-methyldiphenylamine

ll) 2'-Chloro-3-cyclopentyloxy-*N*-(2,6-dichloro-4-pyridylmethyl)-4-methoxydiphenylamine

mm) 3-Cyclopentyloxy-*N*-(2,6-dichloro-4-pyridylmethyl)-4-methoxydiphenylamine

nn) 3-Cyclopentyloxy-4-methoxy-*N*-(6-methyl-2-pyridylmethyl)diphenylamine

oo) 3-Cyclopentyloxy-4-methoxy-*N*-(3-quinolinylmethyl)diphenylamine

pp) 3-Cyclopentyloxy-4-methoxy-*N*-(4-quinolinylmethyl)diphenylamine

qq) 3-Cyclopentyloxy-4-methoxy-*N*-(2-pyrazinylmethyl)diphenylamine

rr) 4-Methoxy-3'-methyl-*N*-(3-pyridylmethyl)-3-(3-tetrahydrofuryloxy)diphenylamine

ss) 4-Methoxy-4'-methyl-*N*-(3-pyridylmethyl)-3-(3-tetrahydrofuryloxy)diphenylamine

tt) 4,4'-Dimethoxy-*N*-(3-pyridylmethyl)-3-(3-tetrahydrofuryloxy)diphenylamine

uu) 3'-Chloro-4-methoxy-*N*-(3-pyridylmethyl)-3-(3-tetrahydrofuryloxy)diphenylamine

vv) 4-Methoxy-4'-(4-methylpiperazin-1-ylcarbonyl)-*N*-(3-pyridylmethyl)-3-(3-tetrahydrofuryloxy)diphenylamine

ww) 3'-Cyano-4-methoxy-*N*-(3-pyridylmethyl)-3-((3*R*)-tetrahydrofuryloxy)diphenylamine

xx) 3'-Cyano-4-methoxy-*N*-(3-pyridylmethyl)-3-((3*R*)-tetrahydrofuryloxy)diphenylamine

yy) 3-Cyclopropylmethoxy-4-difluoromethoxy-*N*-(3-pyridylmethyl)diphenylamine

zz) 3-Cyclopentyloxy-4-difluoromethoxy-*N*-(3-pyridylmethyl)diphenylamine

aaa) 4-Difluoromethoxy-*N*-(3-pyridylmethyl)-3-(3-tetrahydrofuryloxy)diphenylamine

bbb) 3,4-Bis(difluoromethoxy)-*N*-(3-pyridylmethyl)diphenylamine

ccc) 4-Difluoromethoxy-*N*-(3-pyridylmethyl)-3-((3*R*)-tetrahydrofuryloxy)diphenylamine

ddd) 3'-Cyano-4-difluoromethoxy-*N*-(3-pyridylmethyl)-3-((3*R*)-tetrahydrofuryloxy)diphenylamine

eee) 3'-Chloro-4-difluoromethoxy-*N*-(3-pyridylmethyl)-3-((3*R*)-tetrahydrofuryloxy)diphenylamine

fff) Ethyl *N*-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-*N*-(3-pyridylmethyl)-3-aminobenzoate

ggg) 3-Cyclopentyloxy-4-methoxy-3'-(4-methylpiperazin-1-ylcarbonyl)-*N*-(3-pyridylmethyl)diphenylamine

hhh) 3-Cyclopentyloxy-4-methoxy-4'-(4-methylpiperazin-1-ylcarbonyl)-*N*-(3-pyridylmethyl)diphenylamine

iii) 3'-*tert*-Butyldimethylsilyloxy-3-cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

jjj) 4'-*tert*-Butyldimethylsilyloxy-3-cyclopentyloxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

kkk) *tert*-Butyl *N*-(3-cyclopentyloxy-4-methoxyphenyl)-*N*-(3-pyridylmethyl)-3-aminobenzoate

lll) Ethyl *N*-(3-cyclopentyloxy-4-difluoromethoxyphenyl)-*N*-(3-pyridylmethyl)-3-aminobenzoate

mmm) Ethyl *N*-(4-difluoromethoxy-3-(3-tetrahydrofuryloxy)phenyl)-*N*-(3-pyridylmethyl)-3-aminobenzoate

nnn) Ethyl *N*-(3,4-Bis(difluoromethoxy)phenyl)-*N*-(3-pyridylmethyl)-3-aminobenzoate

ooo) Ethyl *N*-(4-methoxy-3-((3*R*)-tetrahydrofuryloxy)phenyl)-*N*-(3-pyridylmethyl)- -3-aminobenzoate

ppp) Ethyl *N*-(3-cyclopropylmethoxy-4-methoxyphenyl)-*N*-(3-pyridylmethyl)-3-aminobenzoate

qqq) 3-Cyclopentyloxy-4-methoxy-4'-(2-(tetrahydropyran-2-yl)-2H-tetrazol-5-yl)-*N*-(3-pyridylmethyl)diphenylamine

rrr) 3-Cyclopentyloxy-4-methoxy-3'-(2-(tetrahydropyran-2-yl)-2H-tetrazol-5-yl)-*N*-(3-pyridylmethyl)diphenylamine

sss) 4-Methoxy-4'-(2-(tetrahydropyran-2-yl)-2H-tetrazol-5-yl)-*N*-(3-pyridylmethyl)-3-((3*R*)-tetrahydrofuryloxy)diphenylamine

ttt) 3-Cyclopropylmethoxy-4-methoxy-4'-(2-(tetrahydropyran-2-yl)-2H-tetrazol-5-yl)-*N*-(3-pyridylmethyl)diphenylamine

uuu) 4-Difluoromethoxy-4'-(2-(tetrahydropyran-2-yl)-2H-tetrazol-5-yl)-*N*-(3-pyridylmethyl)-3-((3*R*)-tetrahydrofuryloxy)diphenylamine

vvv) 3-Cyclopropylmethoxy-4-difluoromethoxy-4'-(2-(tetrahydropyran-2-yl)-2H-tetrazol-5-yl)-*N*-(3-pyridylmethyl)diphenylamine

www) 3-Cyclopentyloxy-4-difluoromethoxy-4'-(2-(tetrahydropyran-2-yl)-2H-tetrazol-5-yl)-*N*-(3-pyridylmethyl)diphenylamine

xxx) 3-Cyclopropylmethoxy-4-difluoromethoxy-3'-(2-(tetrahydropyran-2-yl)-2H-tetrazol-5-yl)-*N*-(3-pyridylmethyl)diphenylamine

yyy) Bis-(3,4-difluoromethoxy)-3'-(2-(tetrahydropyran-2-yl)-2H-tetrazol-5-yl)-*N*-(3-pyridylmethyl)diphenylamine

zzz) 3-*tert*-Butyldimethylsilyloxy-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

aaaa) 3-*tert*-Butyldimethylsilyloxy-3'-chloro-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

bbbb) Ethyl *N*-(3-*tert*-butyldimethylsilyloxy-4-methoxyphenyl)-*N*-(3-pyridylmethyl)-3-aminobenzoate

cccc) 3-Cyclopentyloxy-2'-chloro-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

dddd) 3-(2-indanyloxy)-4-methoxy-*N*-(3-pyridylmethyl)diphenylamine

eeee) tert-Butyl N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-amino-2-chlorobenzoate

ffff) Ethyl N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-2-aminoisonicotinate

gggg) tert-Butyl N-(3,4-Bis-difluoromethoxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoate

hhhh) Methyl N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoate

iiii) N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-bromoaniline (MW 455.35; ESMS *m/z* 455, 457 $(M+H)^+$)

jjjj) tert-Butyl N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-3-amino-6-methylbenzoate

kkkk) tert-Butyl N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoate

llll) N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-3-chloro-4-[2-(2-tetrahydropyranyl)-2H-tetrazol-5-yl]aniline

mmmm) N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-chloro-4-[2-(2-tetrahydropyranyl)-2H-tetrazol-5-yl]aniline

nnnn) N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(N-piperidinylmethyl)aniline (MW 473.613; ESMS *m/z* 474 $(M+H)^+$)

oooo) N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(N-morpholinomethyl)aniline (MW 475.586; ESMS *m/z* 476 $(M+H)^+$)

pppp) N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(N,N-diethyl)aminomethyl)aniline (MW 461.603; ESMS *m/z* 462 $(M+H)^+$)

qqqq) tert-Butyl N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(5-fluoro-3-pyridylmethyl)-4-aminobenzoate

rrrr) tert-Butyl N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(5-(1,3-dimethylpyrazolylmethyl)-3-aminobenzoate

ssss) tert-Butyl N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-5-triflluoromethyl-3-aminobenzoate

tttt) N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(4-(3,5-dichloropyridyl)methyl)-4-[2-(2-tetrahydropyranyl)-2H-tetrazol-5-yl]aniline

uuuu) tert-Butyl N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-6-triflluoromethyl-3-aminobenzoate

vvvv) tert-Butyl N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoate

wwww) N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-3-methylthioaniline (MW 422.546; ESMS *m/z* 423 $(M+H)^+$)

xxxx) N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-methylthioaniline (MW 422.546; ESMS *m/z* 423 $(M+H)^+$)

yyyy) tert-Butyl N-(3-Cyclopentoxy-4-methoxyphenyl)-N-(5-fluoro-3-pyridylmethyl)-3-aminobenzoate

zzzz) tert-Butyl N-(3-Cyclopentoxy-4-methoxyphenyl)-N-(5-fluoro-3-pyridylmethyl)-4-aminobenzoate

aaaaa) tert-Butyl N-(4-Difluoromethoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoate

bbbbb) tert-Butyl N-(3-Cyclopentoxy-4-methoxyphenyl)-N-(2,6-difluorobenzyl)-3-aminobenzoate

ccccc) tert-Butyl N-(3-Cyclopentoxy-4-methoxyphenyl)-N-(4-(3,5-dimethylisoxazolyl))-3-aminobenzoate

ddddd) tert-Butyl N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-amino-5-fluorobenzoate

eeeee) tert-Butyl N-(3-Cyclopentyloxy-4-difluoromethoxyphenyl)-N-(3-pyridylmethyl)-3-amino-5-fluorobenzoate

fffff) tert-Butyl N-(3,4-Bis-difluoromethoxyphenyl)-N-(3-pyridylmethyl)-3-amino-5-fluorobenzoate

ggggg) tert-butyl N-(3,4-bis-difluoromethoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoate

hhhhh) 3,4-Bis(difluoromethoxy)-N-(4-pyrrol-1-ylphenyl)-N-(3-pyridylmethyl))aniline (MW 457.425)

iiiii) 3-Cyclopentyloxy-4-methoxy-N-(3-(1,1-dimethylethoxy)carbonylphenyl)-N-(3-pyridylmethyl)aniline (MW 474.598)

jjjjj) 3-Cyclopentyloxy-4-methoxy-N-(3-pyridyl)-N-(4-(3-chloropyridylmethyl))aniline (MW 409.915)

kkkkk) 4-Methoxy-3-(3R)-tetrahydrofuranyloxy-N-(3-pyridyl)-N-(4-pyridylmethyl)aniline (MW 377.442)

lllll) 3-Cyclopentyloxy-4-methoxy-N-(4-(N',N'-bis(2,4-dimethoxybenzyl)aminosulfonylphenyl))-N-(3-pyridylmethyl)aniline (MW 753.912)

mmmmm) 3,4-Bis(difluoromethoxy)-N-(4-chloro-3-(1,1-dimethylethoxycarbonyl)phenyl)-N-(3-pyridylmethyl))aniline

nnnnn) 4-Methoxy-3-(3R)-tetrahydrofuranyloxy-N-(4-chloro-3-(1,1-dimethylethoxycarbonyl)phenyl)-N-(3-pyridylmethyl)aniline

ooooo) 3-Cyclopentyloxy-4-methoxy-N-(3-(1,1-dimethylethoxycarbonyl)phenyl)-N-(4-(3-chloropyridylmethyl))aniline

ppppp) 4-Methoxy-3-(3R)-tetrahydrofuranyloxy-N-(3-(1,1-dimethylethoxycarbonyl)phenyl)-N-(4-pyridylmethyl)aniline

qqqqq) 3-Cyclopentyloxy-4-methoxy-N-(4-(1,1-dimethylethoxycarbonyl)phenyl)-N-(4-pyridylmethyl)aniline

rrrrr) 3-Cyclopentyloxy-4-methoxy-N-(3-chloro-4-(1,1-dimethylethoxycarbonyl)phenyl)-N-(3-pyridylmethyl)aniline

sssss) 3-Cyclopentyloxy-4-methoxy-N-(4-(1,1-dimethylethoxycarbonyl)-3-methylphenyl)-N-(3-pyridylmethyl)aniline

ttttt) 3-Cyclopentyloxy-4-methoxy-N-(4-(1,1-dimethylethoxycarbonyl)-3-fluorophenyl)-N-(3-pyridylmethyl)aniline

uuuuu) 3-Cyclopentyloxy-4-methoxy-N-(4-chloro-3-(1,1-dimethylethoxycarbonyl)phenyl)-N-(3-pyridylmethyl)aniline

vvvvv) 3-Cyclopentyloxy-4-methoxy-N-(3-(1,1-dimethylethoxycarbonyl)-4-fluorophenyl)-N-(3-pyridylmethyl)aniline

wwwww) 3-Cyclopentyloxy-4-methoxy-N-(3-(1,1-dimethylethoxycarbonyl)phenyl)-N-(4-(3,5-dichloropyridylmethyl))aniline

xxxxx) 3-Cyclopentyloxy-4-methoxy-N-(4-(1,1-dimethylethoxycarbonyl)phenyl)-N-(4-(3,5-dichloropyridylmethyl))aniline

yyyyy) 3-Cyclopentyloxy-4-methoxy-N-(4-(1,1-dimethylethoxycarbonyl)phenyl)-N-(4-(3-chloropyridylmethyl))aniline

zzzzz) 4-Methoxy-3-(3R)-tetrahydrofuryloxy-N-(4-(1,1-dimethylethoxycarbonyl)phenyl)-N-(4-(3,5-dichloropyridylmethyl))aniline

aaaaaa) 4-Methoxy-3-(3R)-tetrahydrofuryloxy-N-(3-(1,1-dimethylethoxycarbonyl)phenyl)-N-(4-(3,5-dichloropyridylmethyl))aniline

bbbbbb) 3-Cyclopentyloxy-4-methoxy-N-(3-(1,1-dimethylethoxycarbonyl)-4-methoxyphenyl)-N-(3-pyridylmethyl)aniline

cccccc) 3-Cyclopentyloxy-4-methoxy-N-(3-(1,1-dimethylethoxycarbonyl)-4-methylphenyl)-N-(3-pyridylmethyl)aniline

dddddd) 3-Cyclopentyloxy-4-methoxy-N-(3-(1,1-dimethylethoxycarbonyl)-4-nitrophenyl)-N-(3-pyridylmethyl)aniline

eeeeee) tert-Butyl N-(3-Cyclopropylmethoxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoate

ffffff) tert-Butyl N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(5-chloro-3-pyridylmethyl)-3-aminobenzoate

gggggg) tert-Butyl N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-fluorobenzyl)-4-aminobenzoate

hhhhhh) tert-Butyl N-(3-Cyclopentyloxy-4-difluoromethoxyphenyl)-N-(3-pyridylmethyl)-4-aminobenzoate,

N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-(4-methylpiperazin-1-yl)sulfonylaniline	MW 536.693	ESMS m/z 537.1 (M+H)+
N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-(4-morpholinyl)sulfonylaniline	MW 523.651	ESMS m/z 524.1 (M+H)+
N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-(4-methylpiperazin-1-yl)sulfonylaniline	MW 536.693	ESMS m/z 537.1 (M+H)+
N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-4-(4-morpholinyl)sulfonylaniline	MW 523.651	ESMS m/z 524.1 (M+H)+
N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-3-(4-methylpiperazin-1-yl)sulfonylaniline	MW 538.666	ESMS m/z 539 (M+H)+
N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-methylpiperazin-1-yl)sulfonylaniline	MW 538.666	ESMS m/z 539 (M+H)+
N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-morpholinyl)sulfonylaniline	MW 525.623	ESMS m/z 526 (M+H)+
N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-3-(4-morpholinyl)sulfonylaniline	MW 525.623	ESMS m/z 526 (M+H)+
N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-ethylpiperazin-1-yl)sulfonylaniline	MW 552.692	ESMS m/z 553 (M+H)+
N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-cyclohexylpiperazin-1-yl)sulfonylaniline	MW 606.784	ESMS m/z 607.1 (M+H)+
N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(3,5-dimethylpiperazin-1-yl)sulfonylaniline	MW 552.692	ESMS m/z 553 (M+H)+
N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-(2-pyridyl)piperazin-1-yl)sulfonylaniline	MW 601.724	ESMS m/z 602 (M+H)+
N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(4-(4-fluorophenyl)piperazin-1-yl)sulfonylaniline	MW 618.727	ESMS m/z 619 (M+H)+
N-(4-Methoxy-3-(3R)-tetrahydrofuranyloxyphenyl)-N-(3-pyridylmethyl)-4-(2,5-dimethylpyrrol-1-yl)sulfonylaniline	MW 533.646	ESMS m/z 534 (M+H)+.

EXAMPLE 7

N-(3-Cyclopentyloxy-4-methoxyphenyl)-*N*-(3-pyridylmethyl)-3-aminobenzoic acid

A solution of 6.5 g of ethyl *N*-(3-cyclopentyloxy-4-methoxyphenyl)-*N*-(3-pyridylmethyl)-3-aminobenzoate in 50 mL of EtOH was treated with 10 mL of 6N NaOH. The mixture was allowed to stand for 6 hours, concentrated, and diluted with 50 mL of H_2O. The aqueous mixture was extracted with 2 x 50 mL of ether, acidified with AcOH to pH 3, and extracted with 2 x 50 mL of EtOAc. The combined EtOAc fractions were washed with 25 mL of H_2O and 25 mL of brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography over SiO_2 (35 g RediSep® column) using a linear gradient of EtOAc and hexanes as eluant (50% EtOAc to 70% EtOAc over 20 minutes) to provide 4.8 g of a yellow solid product after drying in vacuo for 12 h at 60°C. ^{1}H NMR ($CDCl_3$) δ 11.15 (bs, 1H), 8.70-8.55 (m, 2H), 7.77-6.71 (m, 9H), 4.99 (s, 2H), 4.65 (p, J = 3.8 Hz, 1H), 3.84 (s, 3H), 1.86-1.70 (m, 6H), 1.65-1.45 (m, 2H).

The following compounds were prepared in a similar manner as described above:

a) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-*N*-(3-pyridylmethyl)-4-aminobenzoic acid

b) *N*-(3-Cyclopentyloxy-4-difluoromethoxyphenyl)-*N*-(3-pyridylmethyl)-3-aminobenzoic acid

c) *N*-[4-Difluoromethoxy-3-(3-tetrahydrofuryloxy)phenyl]-*N*-(3-pyridylmethyl)-3-aminobenzoic acid

d) *N*-3,4-Bis(difluoromethoxy)phenyl)-*N*-(3-pyridylmethyl)-3-aminobenzoic acid

e) *N*-[4-Methoxy-3-((3*R*)-tetrahydrofuryloxy)phenyl]-*N*-(3-pyridylmethyl)-3-aminobenzoic acid

f) *N*-(3-Cyclopropylmethoxy-4-methoxyphenyl)-*N*-(3-pyridylmethyl)-4-aminobenzoic acid

g) *N*-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-*N*-(3-pyridylmethyl)-3-aminobenzoic acid

h) *N*-(3-Cyclopentyloxy-4-methoxyphenyl)-3-aminobenzoic acid

i) *N*-[3-(4-Chlorophenyl)prop-1-yloxy-4-methoxyphenyl]-*N*-(3-pyridylmethyl)-3-aminobenzoic acid

j) *N*-(3-Cyclopropylmethoxy-4-methoxyphenyl)-*N*-(3-pyridylmethyl)-3-aminobenzoic acid

k) *N*-[3-(2-Indanyloxy)-4-methoxyphenyl]-*N*-(3-pyridylmethyl)-3-aminobenzoic acid

l) *N*-[4-Methoxy-3-(3-tetrahydrofuryloxy)phenyl]-*N*-(3-pyridylmethyl)-3-aminobenzoic acid

m) *N*-[4-Methoxy-3-((3R)-tetrahydrofuryloxy)phenyl]-*N*-(3-pyridylmethyl)-3-aminobenzoic acid

n) *N*-[3-(2-Methoxyethoxy)-4-methoxyphenyl]-*N*-(3-pyridylmethyl)-3-aminobenzoic acid

o) *N*-[4-Methoxy-3-(2-(2-pyridyl)ethyl)oxyphenyl]-*N*-(3-pyridylmethyl)-3-aminobenzoic acid

p) N-(3-(2-Hydroxy)cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid (MW 434.489; ESMS *m/z* 433.5 $(M-H)^-$)

q) N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-2-aminoisonicotinic acid (MW 419.478; ESMS *m/z* (420 $M+H)^+$)

EXAMPLE 8

N-(3-Hydroxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic Acid

N-(3-Cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid (10.0 g, 23.9 mmol) was dissolved in DCM and 22.3 g (167 mmol) of $AlCl_3$ was added. The dark brown solution stirred at room temperature overnight under N_2. The reaction mixture was diluted with 100 mL of DCM and 100 mL of H_2O and the pH of the aqueous phase adjusted to 5.5. The aqueous phase was extracted with 500 mL of EtOAc and the combined organic fractions were concentrated to dryness giving the desired compound.

EXAMPLE 9

Methyl N-(3-hydroxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoate

N-(3-Hydroxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoic acid (7.0 g, 20.0 mmol) was dissolved in 210 mL of MeOH and 2.8 g (36.0 mmol) of acetyl chloride was added. The material was warmed to reflux with stirring overnight. The solution was concentrated in vacuo and then diluted with 200 mL of DCM and washed with saturated NaHCO3, brine, dried (Na2SO4), and concentrated to give 6.85 g (84% yield) of the desired target.

EXAMPLE 10

Methyl N-(3-(2-Hydroxy)cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoate

Methyl N-(3-hydroxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoate (1.2 g, 5.3 mmol), was dissolved in 12 mL of DMF followed by the addition of 1.44 mL (16.5 mmol) of cyclopentyl epoxide and 2.7 g (8.2 mmol) of Cs_2CO_3. The reaction was warmed with stirring to 150°C for 14 hours, cooled to room temperature and 3.5 g of Cs_2CO_3, 0.9 mL of iodomethane and 120 mL of DMF was added to the reaction mixture and stirring continued at 65°C for 12 hours. The mixture was concentrated and purified over SiO_2 using 1.5% MeOH in DCM as eluant.

EXAMPLE 11

N-[3-(3-Hydroxy)cyclopentyloxy-4-methoxyphenyl]-N-(3-pyridylmethyl)-3-aminobenzoic Acid

1 N NaOH (10 mL) was added to a solution of 700 mg (1.56 mmol) of methyl N-(3-(3-hydroxy)cyclopentyloxy-4-methoxyphenyl)-N-(3-pyridylmethyl)-3-aminobenzoate in 10 mL of MeOH and stirred at room temperature for 2 hour. Solvent was removed in vacuo and the residue was dissolved in water, washed with 2 x 10 mL of ethyl acetate, acidified by 1 N HCl to pH 5-6, concentrated down to ~ 10 mL, and back extracted with 3 x 30 mL of MeOH:CH_2Cl_2 (10: 90) three times. The combined organic phase was washed with brine and dried over Na_2SO_4. The filtrate was concentrated in vacuo to dryness leaving the desired compound as an off-white solid foam (650 mg, 96%). [MW 434.489; ESMS *m/z* 433.3 $(M-H)^-$]

The following compounds were prepared in a similar manner as described above:

t-Butyl N-(2-(3-pyridyl)ethy)l-3-aminobenzoate

EXAMPLE 12

_N_-(3-Cyclopentyloxy-4-methoxyphenyl)-_N_-(3-pyridylmethyl)-2-aminobenzoic acid

Tert-Butyl *N*-(3-cyclopentyloxy-4-methoxyphenyl)-*N*-(3-pyridylmethyl)-2-aminobenzoate (60 mg, 0.13 mmol) was taken up in 2 mL 98% formic acid and heated at 40°C for 4 h. The formic acid was removed *in vacuo* and the residue was loaded onto a column of silica gel (RediSep, 4.2 g). The product was eluted with a linear gradient from 40% EtOAc in hexanes to 60% EtOAc in hexanes over 15 min to yield 16 mg of product as a brown solid. ^1H NMR ($CDCl_3$) □ 8.47 (d, 1H, J = 4.9), 8.43 (s, 1H), 8.10 (d, 1H, J = 7.8), 7.67 (d, 1H, J = 7.8 Hz), 7.56 (m, 1H), 7.40-7.20 (m, 3H), 6.75 (d, 1H, J = 8.7), 6.57 (d, 1H, J = 8.7), 6.47 (s, 1H), 4.72 (s, 2H), 4.54 (p, 1H, J = 4.3), 3.77 (s, 3H), 1.80-1.60 (m, 6H), 1.60-1.40 (m, 2H).

The following compounds were prepared in a similar manner as described above:

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Millen, White, Zelano & Branigan, P.C.
2200 Clarendon Blvd.
Suite 1400
Arlington, VA 22201

In re Application of
Schumacher et al.
Application No. 10/622,833
Filed: July 21, 2003
Attorney Docket No. MEMORY-28

DECISION ON PETITION

CASE
ACTION File Petition/Omitted Items
DUE DATE 11/21/04
call up: 10/21/04

This is a decision on the petition filed August 20, 2004, requesting that the above-identified application be accorded a filing date of July 21, 2003, with pages 51-74 of the specification as part of the original disclosure.

On July 21, 2003, applicants filed the above-identified application. On June 21, 2004, the Office mailed a Notice to File Missing Parts of Nonprovisional Application, stating, *inter alia*, that the application had been accorded a filing date of July 21, 2003, and advising applicants that pages 51-74 of the specification appeared to have been omitted.

In response, on August 20, 2004, applicants filed the present petition and a copy of applicants' postcard receipt acknowledging receipt of "NEW ORIGINAL APPLICATION INCLUDING 123 PGS. OF SPEC, 72 PGS. CLAIMS, 1 PGS. ABSTRACT" on July 21, 2003. Unfortunately, applicants failed to submit copies of pages 51-74 of the specification with the present petition.

Accordingly, the petition is **dismissed** without prejudice for reconsideration pending the submission of copies of pages 51-74 of the specification.

Any request for reconsideration must be submitted within TWO MONTHS of the date of this decision and include copies of pages 51-74 of the specification.

dtd. 9/23/04 HW

Further correspondence with respect to this matter should be addressed as follows and to the attention of Senior Petitions Attorney Christina Tartera Donnell:

By mail: Mail Stop Petition
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By hand: U.S. Patent and Trademark Office
220 20th Street S.
Customer Window, Mail Stop Petition
Crystal Plaza 2, Lobby, Room 1B03
Arlington, VA 22202

Any inquiries related to this decision should be directed to the undersigned at (703) 306-5589.

Christina Tartera Donnell

Christina Tartera Donnell
Senior Petitions Attorney
Office of Petitions